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ORIGINAL REPORT

Activity of XL184 (Cabozantinib), an Oral Tyrosine Kinase Inhibitor, in Patients With Medullary Thyroid Cancer

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ABSTRACT

Purpose

XL184 (cabozantinib) is a potent inhibitor of MET, vascular endothelial growth factor receptor 2 (VEGFR2), and RET, with robust antiangiogenic, antitumor, and anti-invasive effects in preclinical models. Early observations of clinical benefit in a phase I study of cabozantinib, which included patients with medullary thyroid cancer (MTC), led to expansion of an MTC-enriched cohort, which is the focus of this article.

Patients and Methods

A phase I dose-escalation study of oral cabozantinib was conducted in patients with advanced solid tumors. Primary end points included evaluation of safety, pharmacokinetics, and maximum-tolerated dose (MTD) determination. Additional end points included RECIST (Response Evaluation Criteria in Solid Tumors) response, pharmacodynamics, *RET* mutational status, and biomarker analyses.

Results

Eighty-five patients were enrolled, including 37 with MTC. The MTD was 175 mg daily. Dose-limiting toxicities were grade 3 palmar plantar erythrodysesthesia (PPE), mucositis, and AST, ALT, and lipase elevations and grade 2 mucositis that resulted in dose interruption and reduction. Ten (29%) of 35 patients with MTC with measurable disease had a confirmed partial response. Overall, 18 patients experienced tumor shrinkage of 30% or more, including 17 (49%) of 35 patients with MTC with measurable disease. Additionally, 15 (41%) of 37 patients with MTC had stable disease (SD) for at least 6 months, resulting in SD for 6 months or longer or confirmed partial response in 68% of patients with MTC.

Conclusion

Cabozantinib has an acceptable safety profile and is active in MTC. Cabozantinib may provide clinical benefit by simultaneously targeting multiple pathways of importance in MTC, including MET, VEGFR2, and RET. A global phase III pivotal study in MTC is ongoing (ClinicalTrials.gov number NCT00215605).

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INTRODUCTION

The development of antiangiogenic agents targeting the vascular endothelial growth factor (VEGF)/ VEGF receptor (VEGFR) signaling pathway has led to key advances in the treatment of cancer. For example, the monoclonal antibody bevacizumab and small-molecule multitargeted VEGFR tyrosine kinase inhibitors (TKIs) sorafenib and sunitinib have produced statistically significant survival improvements in some cancers.[1-3] However, these survival improvements have been modest, and attempts to demonstrate single-agent therapeutic utility across a wide range of cancers have been unsuccessful. A potential explanation for these results may come from recent preclinical and clinical studies indicating that despite providing some short-term clinical benefit, agents targeting the VEGF signaling pathway can ultimately promote tumor aggressiveness, with invasion into neighboring tissues and metastasis to distant sites.[4-7] A mechanism for these untoward effects of anti-VEGF therapy may be the upregulation of MET, a proinvasive receptor tyrosine kinase (RTK) implicated in tumor growth, metastasis, and angiogenesis.[8,9]

Cabozantinib is a potent inhibitor of RTKs, including MET, VEGFR2, and RET.[10,11] In preclinical studies, cabozantinib exhibited significant antiangiogenic and antitumor activity in a broad range of tumor models, including a model of medullary thyroid cancer (MTC) with an activating *RET* mutation. Importantly, it has also been shown in preclinical studies that treatment with cabozantinib results in decreased tumor invasiveness and decreased metastasis compared with either vehicle control or agents targeting VEGF signaling without MET inhibition.[11] This report focuses on results from a phase I open-label dose-escalation study of cabozantinib in patients with a wide range of advanced malignancies, including an expanded cohort of patients with advanced MTC.

Activating mutations in *RET* play a central role in tumorigenesis in both inherited and sporadic forms of MTC. As a component of multiple endocrine neoplasia type 2 syndromes, hereditary MTC comprises 25% to 30% of all MTC cases and is caused by germline gain-of-function mutations in the gene encoding RET.[12] In the sporadic form of the disease, somatic mutations in *RET* occur in 30% to 50% of patients. In addition to RET, MET and its ligand, hepatocyte growth factor, also seem to play significant roles in the pathogenesis of MTC, in which both proteins are frequently coexpressed.[13] Notably, it has been shown that overexpression of MET can be driven by activation of the RET signaling pathway, albeit in a cell type different from that giving rise to MTC.[14] In addition to MET and RET, the VEGF signaling pathway has also been implicated in MTC and is likely involved in disease progression.[15,16]

Patients with metastatic MTC have a poor prognosis, with approximately 25% and 10% alive at 5 and 10 years, respectively.[17] Furthermore, MTC is largely unresponsive to conventional cytotoxic chemotherapy and radiotherapy.[18] Doxorubicin, the only US Food and Drug Administration–approved treatment for patients with advanced thyroid cancer, has resulted in transient tumor response rates in 0% to 20% of patients with MTC and is associated with significant toxicity.[19,20] Although the results of a phase III trial of vandetanib have recently been presented showing improved progression-free survival,[21] there remains an unmet medical need in MTC; no randomized trials have yet been associated with increased overall survival in this patient population.

PATIENTS AND METHODS

Patients

The study enrolled adult patients with histologically confirmed solid tumors or lymphomas that were metastatic or unresectable who were no longer responding to conventional therapies or who had disease for which no standard therapy exists. All patients had an Eastern Cooperative Oncology Group performance status score of 0 to 2 and life expectancy longer than 3 months. Additional parameters for study entry included adequate neutrophil counts ($\geq$ 1,500/μL), platelets ($\geq$ 100,000/μL), hemoglobin ($\geq$ 9g/dL), bilirubin ($\geq$ 1.5 mg/dL), serum creatinine ($<$ 1.5 mg/dL), and ALT and AST ($\leq$ 2.5 $\times$ upper limit of normal with no liver involvement or $\leq$ 5 $\times$ upper limit of normal with liver involvement). Patients were ineligible if they had received chemotherapy or immunotherapy within 4 weeks, nitrosourea therapy within 6 weeks, or radiotherapy or investigational agents within 30 days of the first dose of cabozantinib. Patients with brain metastases, uncontrolled intercurrent illness, or known HIV infection were ineligible. This study was conducted in accordance with the Declaration of Helsinki. Patients provided written informed consent according to institutional guidelines. The study was approved by the institutional review board at each study center.

Study Design and Treatment

Using a three-plus-three study design, patients were assigned to 13 dose levels exploring two different schedules of administration and formulations of cabozantinib. Dose levels one to nine (0.08, 0.16, 0.32, 0.64, 1.28, 2.56, 5.12, 7.68, and 11.52 mg/kg) explored an intermittent schedule (once daily for 5 days followed by 9 days rest) with a suspension formulation, dose levels 10 to 11 (175 and 265 mg) used continuous fixed daily dosing with a suspension formulation, and dose levels 12 to 13 (175 and 250 mg) and the MTD (175 mg) cohort used continuous fixed daily dosing with capsules. All patients were instructed to take cabozantinib in a fasting state (2 hours before and 1 hour after administration of cabozantinib). Patients continued to take cabozantinib until disease progression or unacceptable adverse events. Intrapatient dose escalation was allowed once the MTD was established with the capsule formulation, and dose holds and reductions were allowed for management of adverse events (AEs). Additionally, an expanded MTD cohort that included patients with metastatic and/or locally advanced or locally recurrent MTC not appropriate for surgical resection was initiated.

Table 1. Baseline Patient Demographics and Clinical Characteristics

Characteristic	Entire Cohort (N = 85)	MTC Subset (n = 37)
Age, years		
Median	56	55
Range	24-89	35-72
Sex		
Male	66	31
Female	19	6
Tumor diagnosis, primary site		
Medullary thyroid	37	
Colorectal	8	
Melanoma	6	
Sarcoma*	4	
Pancreatic, carcinoid	3 each	
Mesothelioma, pleomorphic adenoma of salivary glands, gastroesophageal junction, gastric	2 each	
Hepatocellular, liver adenocarcinoma, papillary renal cell, renal cell, parotid, squamous cell carcinoma of tongue, cervical, breast, cutaneous T-cell lymphoma, head and neck/hypopharynx,† appendiceal, laryngeal, neuroendocrine,† adenoid cystic, papillary thyroid, follicular thyroid, esophageal	1 each	
ECOG performance status		
0	34	
1	46	
2	3	
Not reported	2	
Prior chemotherapy		
No. of patients	64	20
Median No. of regimens	3	2
Range	1-13	1-7
No. of patients with prior TKI therapy‡		16
RET mutational status§		31
Germline		3
Somatic		22
Unknown hereditary status		1‖
No mutations detected		5

Abbreviations: MTC, medullary thyroid cancer; ECOG, Eastern Cooperative Oncology Group; TKI, tyrosine kinase inhibitor.
*Including one each of liposarcoma, angiosarcoma, clear cell sarcoma, and alveolar soft-part sarcoma.
†Poorly differentiated.
‡Including 12 patients who had prior RET inhibitors (vandetanib, motesanib, sorafenib, and AEE-788).
§Only activating mutations were scored in this analysis.
‖This patient had an activating mutation in tumor but no corresponding blood sample to determine hereditary status.

Assessment of Safety and Efficacy

AEs were assessed at each visit and graded according to the Common Terminology Criteria for Adverse Events, version 3.0. Safety assessments included an evaluation of the AEs, physical examination, and evaluations of performance status, body weight, complete blood count, serum chemistries, urinalysis, and electrocardiography at regularly scheduled intervals. Dose-limiting toxicity (DLT) was defined as either the occurrence of a treatment-related AE of potential clinical significance such that additional dose escalation would expose patients in higher dose cohorts to risk of irreversible medical harm or require medical treatment to avoid irreversible medical harm or any cabozantinib-related grade 3 or 4 nonhematologic toxicity, including grade 3 nausea and/or vomiting and grade 3 diarrhea despite prophylaxis and/or treatment or the following grade 4 hematologic toxicities: thrombocytopenia, neutropenia of more than 5 days duration, and neutropenia of any duration with fever or documented infection.

Tumor response was assessed by investigators using RECIST (Response Evaluation Criteria in Solid Tumors) at baseline, at 28 days after the first dose of cabozantinib, and every 8 weeks thereafter.[22] Tumor response was confirmed by repeat imaging at least 28 days after the initial response assessment. Pharmacokinetic, calcitonin, carcinoembryonic antigen (CEA), and genotyping analyses were done. A detailed description of the methods is included in the Appendix (online only).

RESULTS

Patients

This study began in September 2005, the last patient was enrolled in August 2008, and a total of 85 patients were enrolled. The results presented here reflect a data cutoff of April 2010. Table 1 shows baseline characteristics of the patient population, including primary tumor sites. Median age was 56 years. Sixty-six of the patients (78%) were male, and 64 of the patients (75%) had prior chemotherapy. The most common tumor diagnosis was MTC (n = 37; 44%). The study population was enrolled across five study centers. Seventy-seven patients with measurable disease according to RECIST were evaluable for response, including 35 patients with MTC. Two patients with MTC had bone metastases or lesions too small to measure by RECIST but were assessable by computed tomography, magnetic resonance imaging, or bone scan. In the MTC subset, a majority of the cases were sporadic (22 [71%] of 31 patients), with three (10%) of 31 patients presenting with inherited MTC (Table 1).

Safety Results

DLTs were observed in three dose levels. In dose level 9 (11.52-mg/kg suspension intermittent dosing cohort), two of three patients experienced DLTs, with one experiencing grade 3 PPE and grade 3 AST/ALT elevations and one experiencing grade 3 lipase elevation. In dose level 11 (265-mg suspension daily dosing cohort), two of 10 patients experienced a DLT of mucositis (one with grade 2 and one with grade 3). In dose level 13 (250-mg capsule dosing cohort), two of six patients experienced DLTs, with one experiencing grade 3 AST elevation and one experiencing grade 3 PPE, thus establishing the next-lowest well-tolerated dose level of 175 mg daily as the maximum-tolerated capsule dose and the dose for the ongoing phase III trial XL184-301.

A total of 77 patients (90%) reported at least one treatment-related AE (Table 2). Of these, 43% reported grade 1 or 2 AEs. The most frequent treatment-related AEs (> 20% of patients) were diarrhea, fatigue, decreased appetite, nausea, PPE, rash, increased AST

Table 2. Treatment-Related Adverse Events

	5 + 9 Suspension (0.08-11.52 mg/kg; n = 33)				Once Daily Suspension (175-265 mg; n = 13)				Once Daily Capsules (175-250 mg; n = 40)				All Patients (any dose; N = 86*)			
	Grade 1/2		Grade 3/4		Grade 1/2		Grade 3/4		Grade 1/2		Grade 3/4		Grade 1/2		Grade 3/4	
Adverse Event	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Diarrhea	12	36	1	3	6	46	2	15	25	63	3	8	43	50	6	7
Fatigue	9	27	2	6	8	62	2	15	22	55	5	13	39	45	9	10
Decreased appetite	8	24	—	—	7	54	—	—	25	63	1	3	40	47	1	1
Nausea	9	27	—	—	7	54	—	—	20	50	1	3	36	42	1	1
Palmar plantar erythrodysesthesia	1	3	1	3	5	38	—	—	11	28	8	20	17	20	9	10
Rash	7	21	—	—	3	23	—	—	12	30	—	—	22	26	—	—
Increased aspartate aminotransferase	4	12	1	3	4	31	—	—	11	28	2	5	19	22	3	3
Vomiting	4	12	—	—	2	15	—	—	15	38	—	—	21	24	—	—
Mucosal inflammation	5	15	—	—	6	46	1	8	9	23	—	—	20	23	1	1
Hair color changes	4	12	—	—	4	31	—	—	11	28	—	—	19	22	—	—
Increased alanine aminotransferase	4	12	1	3	1	8	—	—	11	28	2	5	16	19	3	3
Oral pain	2	6	—	—	4	31	—	—	10	25	—	—	16	19	—	—
Decreased weight	3	9	1	3	4	31	1	8	8	20	1	3	13	15	5	6
Dysgeusia	1	3	—	—	2	15	—	—	11	28	—	—	14	16	—	—
Hypertension	3	9	—	—	1	8	—	—	8	20	2	5	12	14	2	2
Dry skin	1	3	—	—	—	—	—	—	9	23	—	—	10	12	—	—
Peripheral neuropathy	1	3	—	—	5	38	—	—	4	10	—	—	10	12	—	—
Increased lipase	—	—	1	3	1	8	1	8	3	8	7	18	4	5	9	10
Increased blood amylase	1	3	1	3	—	—	—	—	4	10	3	8	5	6	4	5

NOTE. Adverse events occurring in at least 10% of patients.
Abbreviation: 5 + 9, once daily for 5 days followed by 9 days rest.
*No. of patients is 86 because one patient withdrew consent and subsequently re-enrolled onto trial; this patient is counted twice in safety data.

Table 3. Tumor Response in Patients With MTC According to RECIST

Tumor Response	MTC Subset (n = 37)	Time to Response (days)	Duration of Response (months)
No. of patients evaluable for response	35*		
Complete	0		
Partial	10		
Median duration of response, months (range)	Not yet reached		
Range	4-35+		
Median follow-up, months	17+		
Median time to tumor response, days	50		
Range	21-365		
Stable disease, ≥ 6 months	15		
Duration of partial response			
Patient			
1		24	3.9
2		28	4.1
3		21	4.5
4		117	8.3
5		27	13.2
6		365	7.3†
7		24	18.3†
8		71	18.9†
9		85	33.9†
10		79	34.7†

Abbreviations: MTC, medullary thyroid cancer; RECIST, Response Evaluation Criteria in Solid Tumors.
*Two patients had nonmeasurable disease.
†Active patient with continued confirmed partial response.

level, vomiting, and mucosal inflammation. One grade 4 event (pulmonary embolism, dose level 10, 175-mg suspension daily dosing) was assessed as related to cabozantinib. Treatment-related hypertension of grade 3 severity occurred in two patients (2%) and of grade 1 to 2 severity occurred in 12 patients (14%), most of whom had a history of hypertension. There were no treatment-related grade 5 events, and the nature of AEs was similar between patients with MTC and those with other solid tumor diagnoses.

Response

Of the 35 patients with MTC with measurable disease, confirmed objective response was achieved in 10 (29%; 95% CI, 15% to 45%), each of whom had a partial response (Table 3). Five of the 10 responders had a partial response at the first radiologic assessment, and responses occurred most commonly at the 175-mg dose level. Overall, 17 patients (49%) experienced a 30% or greater decrease in the sum of tumor measurements compared with baseline measurements (Fig 1A), including seven patients without confirmed response resulting either from lack of response based on the subsequent confirmatory scan or from study discontinuation before the subsequent scan. Stable disease of at least 6 months duration (range, 6.4 to 31.1 months) was observed in 15 (41%) of the 37 patients with MTC.

Stable disease of at least 6 months or confirmed partial response was observed in 25 (68%) of 37 patients with MTC. Onset of tumor response in the MTC population was reported as early as day 21 and as late as day 365. Median time to response was 49.5 days, whereas the median duration of response has not yet been reached (range, 3.9 to > 35 months) with a minimum of 17 months of follow-up. Of the 20 (54%) of 37 patients with MTC who had received prior therapy, 16 (43%) of 37 were treated with TKIs (Table 1). Three of the 10 responses occurred in patients with MTC in whom prior TKI therapies had failed, including those known to inhibit RET (eg, vandetanib and sorafenib),[23-27] as well as in patients who had previously received treatment with cytotoxic chemotherapy.

For the non-MTC subset, stable disease of at least 3 months was reported in 38% of patients (Fig 1B). This included the following tumors: colorectal (three patients), melanoma (two patients), and carcinoid (two patients) tumors and adenoid cystic, follicular thyroid, papillary thyroid, hepatocellular, renal cell carcinoma, cutaneous T-cell lymphoma, salivary gland, alveolar sarcoma, clear-cell sarcoma, mesothelioma, and neuroendocrine tumor originating in the thyroid (one patient each). The patient with a neuroendocrine tumor originating in the thyroid also experienced tumor shrinkage of more than 30% (Fig 1B).

Genotyping Analyses

Germline and somatic *RET* genotyping for the patients with MTC was performed using DNA isolated from whole blood (n = 30) and tumor (n = 31), respectively. Activating *RET* mutations were detected in tumors from 25 (81%) of 31 patients with MTC (Table 1; Fig 1). Notably, the tumor of one patient with rapid clinical progression exhibited no detectable *RET* mutation in the analyzed clinically relevant mutational hotspots; however, a *BRAF* activating mutation (G469A) and a 2.2-fold amplification of the gene encoding MET were detected (Appendix Table A1, online only). Of the four remaining patients without detectable *RET* hotspot mutations, one was found to have a 1.7-fold amplification of *MET* in the tumor. In addition, sequence analysis of *MET* in tumor DNA from a subset of patients with MTC (n = 15) did not reveal any mutations (Appendix Table A1). A strict correlation was not observed between *RET* mutational status and either clinical response or time on study.

Pharmacokinetics

The peak plasma concentration and area under the plasma concentration-time curve up to the last quantifiable time point for cabozantinib increased in proportion to dose in the individual dosing cohorts. After repeat daily dosing, terminal half-life values (mean ± standard deviation) for cabozantinib were 91.3 ± 33.3 hours (n = 23), and apparent steady-state plasma levels were reached by day 15. Steady-state clearance for the 175-mg capsule dose derived from repeat dose data was 4.2 ± 1.5 L/h. Patients receiving 175-mg cabozantinib capsules had four- to five-fold higher steady-state exposure (area under the curve) compared with day 1 (7.68 ± 2.85 μg * h/mL; n = 23 *v* 41.6 ± 15.5 μg * h/mL; n = 23), indicating that cabozantinib accumulated with repeat daily dosing (Appendix Table A2, online only). There was no significant difference in exposure between patients with MTC and those without MTC.

Other Biomarker Analyses

Reductions in serum calcitonin ranging from 3% to 99% below baseline were observed in 28 of 30 patients with any measurable tumor shrinkage (Fig 2). Of the 28 patients with CEA data and measurable disease, 24 had a reduction in CEA ranging from 13% to 94% below baseline.

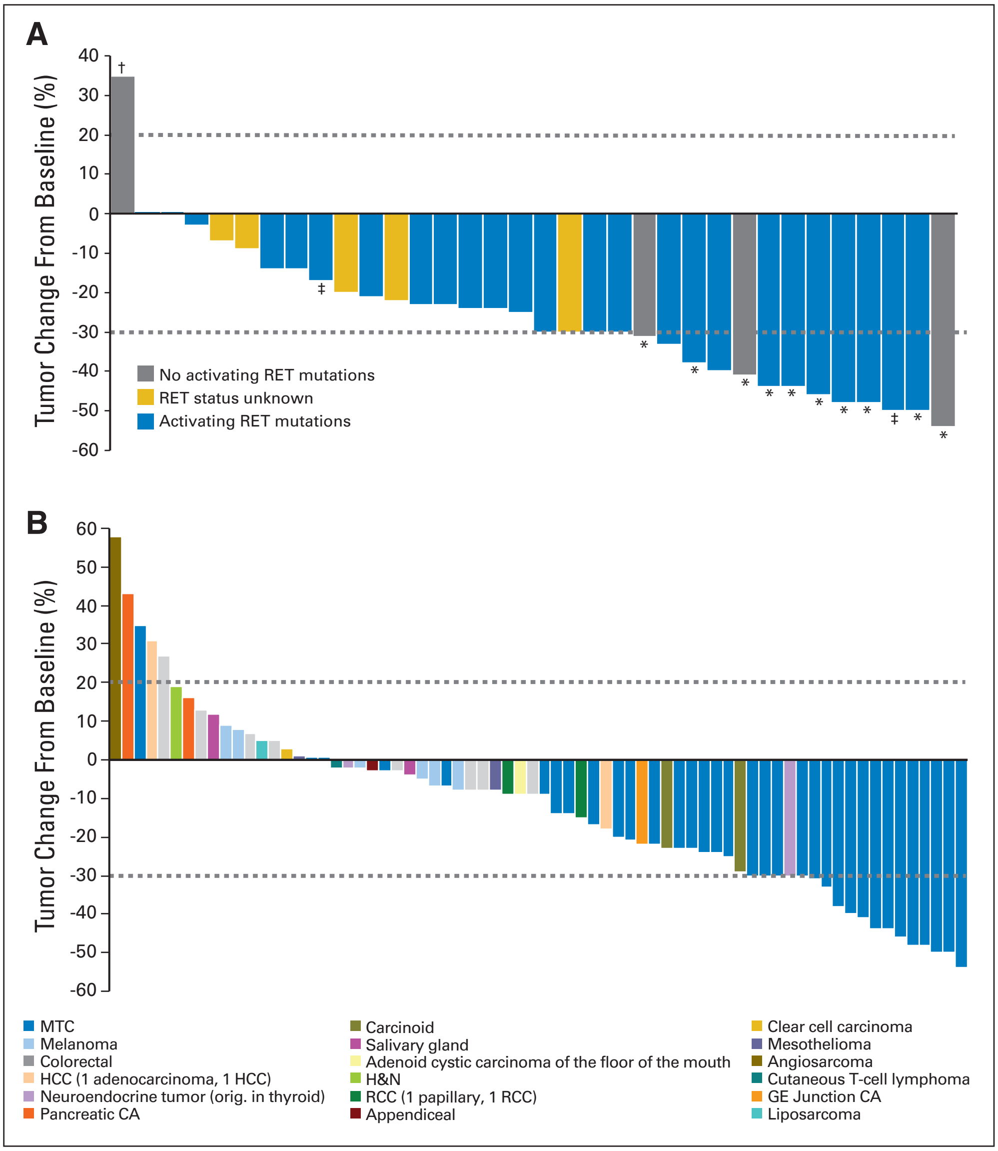

Fig 1. (A) Best radiologic response in patients with medullary thyroid cancer (MTC) with one or more postbaseline scans (n = 34). Scan data available for 34 patients with MTC with measurable disease and at least one postbaseline scan. Two patients had nonmeasurable disease, and one patient had no postbaseline scan. (*) Confirmed partial response per Response Evaluation Criteria in Solid Tumors (RECIST). (†) Patient with MTC and G469A BRAF mutation. (‡) Germline RET mutation. (B) Best radiologic response in all patients with one or more postbaseline scan (n = 70). Scan data available for all patients with measurable disease and with at least one postbaseline scan. Eight patients had nonmeasurable disease and are not represented in this graph. An additional seven patients had no postbaseline scan and are also not represented in this graph. HCC, hepatocellular; CA, carcinoma; H&N, head and neck; RCC, renal cell carcinoma; GE, gastroesophageal.

Changes were observed in the levels of circulating biomarkers related to the mechanism of action of cabozantinib, including placental growth factor, VEGF-A, soluble VEGFR2, erythropoietin, and soluble MET (Appendix Fig A1, online only). In addition, decreased phosphorylation of MET and RET was observed in skin biopsies obtained from one patient with MTC (Appendix Fig A2, online only).

DISCUSSION

This phase I study of cabozantinib demonstrated that the drug is active in MTC, with an acceptable spectrum of toxicity. MTC is a neuroendocrine malignancy arising from parafollicular calcitonin-producing C cells, a neural crest-derived tissue that normally expresses the RET RTK.[26,28] A detailed understanding of the molecular lesions associated with MTC has spurred development of new therapeutic approaches for patients with metastatic disease. RTK inhibitors targeting RET and/or VEGFR2 have been reported to result in partial response rates as high as 20% in this disease.[23-25,29-31] Cabozantinib is among the first molecules in the class of dual RET/VEGFR2 inhibitors to also inhibit MET, an RTK that is overexpressed in many human tumors, including those of the thyroid epithelium.[13] On the basis of preclinical data, this attribute of cabozantinib may result in decreased tumor invasiveness and metastatic spread compared to VEGF pathway inhibition without MET inhibition.[11]

Frequently reported AEs of cabozantinib are largely consistent with those of other agents that target RTKs, including VEGFR2, KIT, and RET.[24,25,31] The incidence of hypertension (16% all grades, including 2% grade 3) reported in this study (Table 2) is lower than expected, compared with the incidence of treatment-related hypertension in recent studies with other TKIs, including motesanib[29] and axitinib.[32]

The confirmed partial response rate of 29%, rapidity of response, and prolonged duration of response observed in a largely heavily pretreated population of patients with MTC that included prior TKI/RET-inhibitor therapy, including vandetanib, compares favorably

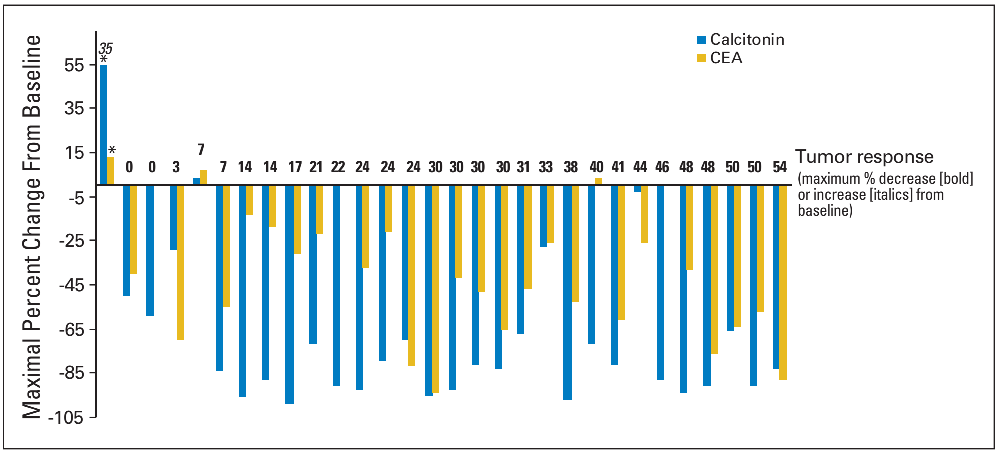

Fig 2. Relationship between maximal tumor shrinkage and maximal decrease in calcitonin and/or carcinoembryonic antigen (CEA) in patients with medullary thyroid cancer (MTC; n = 30). Lack of correlation between maximal tumor shrinkage and maximal change in calcitonin and/or CEA in patients with MTC with complete calcitonin and CEA measurements and with measurable disease. (*) Bars represent a patient with MTC who had a *BRAF* mutation but no known *RET* mutation and progressed rapidly. This patient did not demonstrate a decrease in calcitonin or CEA from baseline values.

with efficacy reported in other trials of TKIs in MTC.[23,25,31,33] However, the clinical significance of the reported prolonged stable disease in this patient group is uncertain because of the lack of evidence of disease progression before study entry. Fifty-four percent of patients with MTC had received prior therapy (Table 1), including 16 patients (43%) who were treated with TKIs. One patient with MTC harbored an activating *BRAF* mutation, a rare finding in this disease group.[33] BRAF is known to signal downstream of the RTKs targeted by cabozantinib, which may account for the lack of response in this patient (Figs 1A and B).

Evidence of tumor regression was observed in patients with and without identified *RET* mutations in the analyzed clinically relevant mutational hotspots, suggestive of anticancer effects potentially attributable to inhibition of targets other than RET, such as MET and/or VEGFR2, or to as yet unknown aberrations in the RET pathway. Notably, evidence of durable tumor shrinkage or stable disease was observed in 12 of 15 patients with MTC with a somatic M918T mutation in *RET* (treatment duration range, 6 to 38 months), which has been shown to be a strong negative prognostic indicator for metastasis-free and overall survival.[34] This degree of durable response in patients with the M918T mutation contrasts with the limited clinical benefit of motesanib, a RET and VEGFR inhibitor, in similar patients.[29]

Exposure to cabozantinib resulted in significant changes in levels of the circulating biomarkers placental growth factor, VEGF-A, soluble VEGFR2, and erythropoietin, consistent with changes observed with other antiangiogenic agents.[35] Levels of soluble MET in plasma increased during treatment, a finding consistent with preclinical observations made with a MET-targeted monoclonal antibody,[36] and an analysis of skin samples from a patient with MTC revealed decreased phosphorylation of MET and RET after administration of cabozantinib. In addition, although calcitonin and CEA generally decreased from baseline in patients with any measurable tumor shrinkage (Fig 2), a significant correlation between the magnitude of tumor reduction and magnitude of reduction of calcitonin was not observed. The lack of correlation between calcitonin changes and tumor reduction may be the result of a pharmacodynamic effect of cabozantinib on RET, in that RET is known to mediate calcitonin secretion via modulation of calcitonin gene transcription.[37]

In summary, these phase I results indicate that cabozantinib is active in patients with MTC, including those who harbor somatic *RET* mutations and are potentially at high risk for progression and death.[34] Cabozantinib has an acceptable safety profile and dose-dependent exposure and half-life supporting once daily dosing, with only moderate inter-individual variability. Future studies will evaluate the need for administration of the drug in a fasting state. Furthermore, cabozantinib is active in patients who have progressed while receiving prior therapies, including other inhibitors of RET and VEGFR2. An international phase III study of cabozantinib is ongoing in patients with progressive MTC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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